Declaration of Dr. Benjamin G. Cameransi, Jr. M.D.

1. I am Board Certified in Anesthesiology as a Diplomate of the American Board of Anesthesiology. I practice anesthesiology at Waccamaw Community Hospital in Murrells Inlet, SC, where I have served as Medical Director of Anesthesiology for over five years. I have practiced as an attending anesthesiologist in large community hospitals since 1999. I am trained in the recognition and treatment of anesthesia induced malignant hyperthermia. My Curriculum Vitae is attached hereto as Exhibit A.

2. I am a founder and principal of Lyotropic Therapeutics, Inc. Among my responsibilities are to plan and oversee in vivo studies for the company's anesthesia products under development, including its high concentration, low volume safe for injection dantrolene sodium product. I have been involved with all aspects of the work of Lyotropic Therapeutics, Inc. in developing its a low volume, high concentration, safe for injection reformulation of sodium dantrolene, specifically described as follows: an initial effective dose (approximately 150 – 300 mg, depending upon patient weight) will be administrable by a single injection of less than 10 cc, after a single mixing step of lyophilized product with sterile water for injection, in less than one minute.

3. For nearly ten years in particular I have carefully followed and studied the use and development of pharmaceutical formulations of dantrolene. I have read hundreds of research and clinical articles, and discussed findings with key experts in the field, including the use of injectable dantrolene in the treatment of malignant hyperthermia, and the work and recommendations of the Malignant Hyperthermia Society of the United States (MHAUS). I have done this in pursuit of a low volume, high concentration safe for injection formulation of dantrolene, because of the beneficial impact it would make on clinical outcomes in the United States and around the world.

4. From my familiarity with the research and clinical literature, my experience in the clinic, and my frequent discussions with other experts in the field, I am aware that a high

concentration, low volume, rapidly administrable safe for injection formulation of dantrolene would mark a significant clinical improvement in the treatment of anesthesia induced MH. I am aware that there has been a long felt need for such a formulation, due to the limitations of the available marketed product, which is high volume, low concentration, extraordinarily difficult to reconstitute in a thorough and timely manner, and time consuming to administer. The availability of such a new formulation would make a significant impact on clinical outcomes, reducing morbidity and mortality associated with malignant hyperthermia.

5. Anesthesia – induced MH is the nightmare of practicing anesthesiologists. This life threatening clinical crisis presents abruptly and progresses rapidly. It is caused in a small number of patients by the administration of a combination of common, and indeed preferred, anesthetic agents. Literally within moments, a normal operating room experience can be transformed into a life threatening crisis response. The MH crisis endangers multiple organ systems and demands timely recognition, and timely and aggressive treatment with dantrolene together with supportive measures. Systemic skeletal muscle contractions and increased metabolism in muscle drive the MH crisis cascade, causing elevated CO2, acidosis, cell damage and accumulated metabolic waste products. Administration of a therapeutic amount of dantrolene specifically decreases intracellular calcium in muscle cells thus interrupting skeletal muscle contractions and increased metabolism and so terminating the MH crisis.

6. In an MH crisis, the risks of morbidity and mortality increase as a function of time and indeed often at an accelerating rate, for several reasons. First, muscle contraction itself increases the difficulty of successfully treating the crisis, as it diminishes perfusion of the contracting muscle tissue mass and increases the amount of time required for a given dose of dantrolene to have effect. Second, as a result of acidosis and increasing serum potassium levels, cardiac arrhythmias appear and increase over time, frequently resulting in ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation and pulseless electrical activity (which may result in death). Third, temperature and acid pH in muscle cells further impair the ability of the cell to control

intracellular calcium concentrations. Fourth, rise in body temperature generally presents at late stages of the crisis, and when present temperature may increase at a rate of 1° C per 5 minutes. Therefore any delay whatsoever in administration of dantrolene directly increases the risk of highly elevated body temperatures. Body temperatures in excess of 104° F are not uncommon in MH cases in which dantrolene administration is not immediate; temperatures in this range generally are associated with cerebral swelling with a potential for brain damage and multiorgan system failure. A reduction in time in the order of 10 to 20 minutes in completing the delivery to the patient the full initial therapeutic dose of dantrolene would in my opinion reduce the risk and incidence of morbidity and mortality.

7. A formulation that reduces the time required to prepare and complete the administration of a full therapeutic dose of dantrolene to less than five minutes, and preferably less than one minute, and consequently reduces the time during which patients are exposed untreated to the life threatening cascade of increasingly noxious physiologic events that constitute the MH crisis would unquestionably reduce the risk of morbidity and mortality from MH. In my opinion such a formulation would be a major therapeutic advance in the management of MH.

8. Delays in diagnosis and lack of patient monitoring historically have been factors addressed in improving clinical outcomes, and we now enjoy increased preparedness and improved patient monitoring technology. However, despite these advances, the diagnosis of MH in clinical presentation is often made late in the crisis. This is because the first clinical signs of MH frequently are not specific, and there are many considerations which delay definitive diagnosis. The persistence of this delay underscores the clinical significance of any improvement that reduces the time in which a therapeutic dose of dantrolene can be administered.

9. Several factors support the conclusion that the phenomenon of delayed recognition of MH in the clinic is likely to continue and very possibly increase. First, the use of anesthesia triggering agents has spread widely to locations other than dedicated

hospital based specialty surgical suites, for example, to ambulatory surgical centers and physician offices. In these new settings, the clinical staff is less likely to be experienced in and trained and prepared for rare complications in the course of anesthesia, and less prepared to diagnose and initiate treatment of MH. In such settings, it is plausible to postulate that the thorough and time consuming process of taking personal history to identify in advance patients with a predisposition to MH is less likely to occur or to be as thorough or as successful in obtaining accurate information, as in major medical centers. In addition, due to the nature of some of the more common procedures typically performed in these settings, clinicians may be deprived of clinical data which would provide early warning of the MH crisis: such is the case in laparoscopic surgeries where insufflation of the cavity is achieved by introducing CO2 under pressure. In this instance, CO2 is systemically absorbed and expired via respiration and heart rate is actively managed by administration of betablockers. The clinician therefore is deprived of easy recognition of rapid heart rate, typically one of the initial signs of an MH crisis. In most surgeries in these settings, CO2 monitoring is performed by end-tidal gas measurement. In addition, multiple studies over the years show that a very significant number of ambulatory surgical centers and physician offices using triggering anesthetics simply do not have dantrolene on hand. In these circumstances, the only course of treatment involves considerable delay – either a transfer to a dantrolene equipped facility, or retrieval of dantrolene from such a facility.

10. The marketed product, Dantrium IV® (and its recently introduced generic equivalent) has significant clinical limitations arising from the very nature of the formulation. As set forth in the U.S. Patent Application Serial No. 10/788,413, it is an extraordinarily cumbersome formulation. As beneficial as the introduction of this crude formulation has been, it is infamous for its cumbersome, bulky, multiple step, complex and time-consuming protocol for preparation and administration for treatment of a rapidly progressing life threatening crisis. In the face of the time critical MH crisis response, clinicians must devote a significant amount of time, attention and personnel is required to locate, retrieve, prepare and administer a single therapeutic dose of Dantrium IV. The complexity of the required preparation introduces significant risks of error. A

significant simplification in the process of preparation and administration of dantrolene or a significant reduction in the time to administer a full effective therapeutic dose, or both, would constitute a clinically significant improvement for the patient and anesthesiologist.

11. The administration, as well as the reconstitution, of Dantrium IV is a slow process. For a 70 kg patient, the initial therapeutic dose of 2.5 – 3.0 mg /kg recommended by MHAUS would require administration of a very large volume of fluid, over 500 ml. My experience is that administration of this amount of fluid with standard IV tubing sets requires approximately 20 minutes after the time Dantrium has been reconstituted and is ready for administration. Because of this long time and the universal recognition that dantrolene should be administered as rapidly as possible, treatment protocols recommend "pushing" in the formulation if possible. Where this can be accomplished, the time to administration of the full therapeutic dose can be reduced approximately in half, to approximately 10 minutes. However, pushing in the dose is not possible in all cases, for example, where large capacity veins are not available, for children, for elderly, and in certain procedures such as head and neck surgery. Moreover, rapid bolus administration of the dose can cause its own problems. A vein can rupture from pressurized injection, it can spasm and become lumenally occluded, clotting can be induced which can mechanically block the vein as well as create pulmonary emboli: these are not only problematic in their own right, but also may foreclose the established venous access for the administration of dantrolene. Extravascular administration of dantrolene with mannitol as part of its formulation has been associated with compartment syndrome.

12. Morbidity includes relapse, which is related to the length of time from the first sign of MH to the initiation of dantrolene administration was significantly greater (63.6 minutes) in patients who experienced a relapse of MH than those who did not (54.1 minutes) ($p<0.001$). Morbidity also includes hyperkalemia; renal dysfunction; pulmonary edema; coagulopathy and altered level of consciousness (indicative of cerebral edema) (10%). Cerebral damage incident to MH is caused by prolonged elevation in cranial temperature, with the threshold estimated at 104° F. Body

temperature escalation generally occurs later in an MH crisis, but once it appears, can escalate as much as 1° C every five minutes. Long term kidney damage was reported in 4% of the Registry cases. Kidney damage is due to the accumulation in the kidney of myoglobin, a by product of muscle cell breakdown. The amount of kidney damage in my opinion is a function of three factors: how quickly an effective dose of dantrolene was administered, the pH of the urine and the hydration status of the patient. Phlebitis was reported in 10% of the Registry cases. Phlebitis is due to a number of factors in the context of an MH crisis, among which are the need to administer a large volume of Dantrium IV as quickly as possible, the lengthy dwell time at the site of injection (from an infusion of 10 to 20 minute or more), and the tendency to push the large volume injection in order to deliver it more rapidly. In my opinion, delivering the identical dose of dantrolene in a single push of 10 cc or less could be expected to significantly reduce the incidence of phlebitis. Delivering the identical dose of dantrolene without the time consuming and distracting requirements of reconstitution and administration, that is by one person in one minute or less, would make significant improvement to clinical outcomes of those who suffer an MH crisis.

13. The simpler overall protocol for preparing and administering the new dantrolene formulation of the referenced application, as compared to Dantrium IV itself, represents a significant clinical improvement. Virtually any reduction in the complexity or number of steps or variables or components incumbent upon preparation of Dantrium IV will be reflected in an improvement in patient safety and efficacy, as it reduces the risk of error. In this case, I am assuming that the new formulation, Ryanodex®, will be prepared on site by withdrawing sterile water for injection from a 10 ml vial. By contrast, a single therapeutic dose of Dantrium IV is prepared by mixing six separate vials of lyophilized powder with large volumes (one half liter and more) of sterile water for injection. In the surgical suite, it is common to prepare medications with small amounts of sterile water for injection; however, it is rare, if not unique to Dantrium IV, to use very large amounts. Indeed, administration of large volumes of sterile water for injection is contraindicated in most clinical situations. The very presence of one liter bags of sterile water for injection in the surgical suite is cause for a potentially dangerous error and, conversely, the

common presence of normal saline or lactated Ringers' lactate in identically sized and shaped one liter bags, is cause for error in the preparation of Dantrium IV.

14. The well documented and widespread absence of dantrolene from facilities such as ambulatory surgical centers and physician offices in which MH triggering anesthetic agents are administered appears to be the result of a complex set of reasons. One of these is thought to be the unusual, bulky, high volume nature of the formulation. A reformulation that is available in an easier to use, low volume syringe would in my opinion be readily accepted and lead to an increase the availability of dantrolene to additional settings.

15. (a) I am aware of one previous attempt to develop a low volume high concentration injectable formulation of dantrolene in the mid 1990s, reported in Anesthesia & Analgesia 1996: 82: 796-802 by Karan et al. As I have over the years on a number of occasions, I recently spoke with Dr. Sheila Muldoon, one of the investigators on the Article, concerning the Article and the experimental work on which the Article reported. Dr. Muldoon authorized me to relay the conversation in this Declaration. This work failed in in vivo testing and was discontinued.

(b) Dr. Muldoon, at the time of the experimental work reported in the Article, was Chairman of the Department of Anesthesiology, Uniformed Serviced University of the Health Sciences ("USUHS"), Bethesda, Maryland. She participated in the work because of the extreme clinical importance she attached to finding a low volume, high concentration, safe for injection, quickly administrable formulation of dantrolene sodium, in particular, given her responsibilities in the context of the surgical needs of the military. Dr. Muldoon since has retired from Chairmanship, and currently is full professor in the Department of Anesthesiology at USUHS.

(c) The experimental work on the formulation reported in the Article was terminated at or shortly after the publication of the Article because of events arising after submission of the Article: the continuing and insurmountable inability of the lecithin

coated microcrystal technology to reliably prepare a formulation of dantrolene of certain, safe and stable particle size and certain and efficacious concentration, and the extensive pulmonary damage caused to animals administered such formulation. This conclusion applied to both the dantrolene sodium (MC-NaD) and the neutral dantrolene (MC-D) variants of the formulation. While the final paragraph of the published Article states in effect that the incomplete data reported in the Article "suggests" that MC-D "may be" a viable candidate formulation, further information developed on the work reported therein and further experience of the investigators themselves conclusively demonstrated to the investigators that it was not. This conclusion was reported to their peers, and all work was terminated, and no further work on the formulation ever done.

(d) The investigators couldn't develop a reliable production process. As a result, batch to batch particle size was highly variable, including many excessively large particles. The particles were not stable, and readily aggregated. Furthermore, the problems of post-reconstitution filtration, upon examination, proved unsolvable. Post–reconstitution filtration proved inconsistent and ineffective in assuring safe particle and crystal size. Various filtration methods which were attempted, but they removed varying amounts and concentrations of material and API, and yielded dispersions of varying and often unsafe particle size and varying API concentration, often resulting in a filtered product containing less than effective dosage concentrations and amounts.

(e) Furthermore, information developed subsequent to the submission of the manuscript for publication based on gross necropsy of swine receiving injections of the various formulations revealed substantial and widespread yellow-orange colored staining of the lung parenchyma. This was caused by the blockage of pulmonary blood vessels by excessively sized particles and dantrolene crystals from the formulations. This was true for both MC-NaD and MC-D formulations administered, including filtered formulations: all showed unacceptable levels of occlusion in the vessels in the lungs. These autopsies revealed embolic phenomenon much more significant than that reported in the Article, and patently unsafe.

(f) While undertaking the experimental work, Dr. Muldoon and other investigators, because of its importance, had reported early results to the Orphan Drug Office of the Food and Drug Administration and received encouragement. In 1995/1996, after the publication of the Article and after the further analysis and the additional data and experience set forth above, Drs. Muldoon and Karan notified the Orphan Drug Office that the formulation was not viable, and all work was being discontinued. Around the same time she notified other colleagues and leaders in the field, including Dr. Henry Rosenberg, Chairman of the Malignant Hyperthermia Association of the United States, and one of the world leaders in MH research, Dr. Frank Wappler, of the failure of the formulation and decision to terminate further experimental work.

(g) Dr. Muldoon continues to believe today, as she did at the time that the experimental work reported in the Article was ongoing, that there is a pressing, important and as yet unmet clinical need for a high concentration, low volume, safe for injection, quickly administrable formulation of dantrolene, which would be met by the formulation specified in the Instant Invention.

16. In <u>in vivo</u> studies of injectable products, the porcine model is well accepted in the literature and by those skilled in the art as being a highly sensitive indicator of potential cardiopulmonary complications arising from particle size, aggregation, recrystallization and the like, and a reliable source of data for safety in humans. By contrast, dog models are significantly less sensitive and less reliable, because the pulmonary circulation is considered by some to be more compliant in response to increases in pulmonary pressures resulting from increases in intravascular volume, embolic phenomena, elevated systemic blood pressures and/or right heart failure when compared to human pulmonary physiology.

17. The availability of dantrolene for oral administration in no way addresses the long felt need for a low volume, fast acting dantrolene formulation suitable for treating MH. This is because an oral formulation is unsuitable for use in treating MH crisis. In such a crisis the patient is under deep sedation or anesthesia, and the oral administration of any

drug is contra indicated, not only because it is difficult if not impossible to accomplish with the sedated patient, it also introduces risk of airway obstruction. Furthermore, the administration of any drug into the upper GI tract will result in slow and variable absorption and unpredictable plasma concentrations. Given the nature of the MH attack, the administration of the antidote must by direct injection. There has been an acute need for many years for a low volume, high concentration, quickly administered injectable product suitable to administration to a patient in MH crisis, and no product of which I am aware satisfies these needs.

18. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Benjamin G. Cameransi

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12-11-2008

Date

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PROFESSIONAL CLINICAL EXPERIENCE

Seaside Anesthesia Consultants, LLC
Waccamaw Community Hospital, Murrells Inlet, South Carolina
August 2003 to present
Medical Director, Anesthesiology
Attending Anesthesiologist

Sand Hills Anesthesia, LLC
Carolina Pines Regional Medical Center, Hartsville, South Carolina
April 2001 to July 2003
Founding Partner & Medical Director, Anesthesiology
Attending Anesthesiologist

Florence Anesthesia Associates, LLC
Hospital of the Carolinas, Florence, South Carolina
July 1999 to April 2001
Attending Anesthesiologist

Pennsylvania State University College of Medicine
Hershey Medical Center, Hershey, Pennsylvania
July 1996 to July 1999
Department of Anesthesiology
Post Graduate Years II to IV, Residency Training
Julien F. Biebuyck, M.B., Chairman (retired)
Garfield Russell, M.D., Chairman (acting)

Greater Baltimore Medical Center, Baltimore, Maryland
July 1995 to July 1996
Department of Medicine
Post Graduate Year I, Preliminary Year, Internship
Thomas F. Lansdale, III, M.D., Chairman

PROFESSIONAL Non-CLINICAL EXPERIENCE

PharmaKinetics Laboratories, Inc., Baltimore, Maryland
January 1995 to June 1995
Clinical Operations & Exploratory Business Development. Assisted in the design and management of early Phase I & II human clinical studies for Specialty Pharma and Bio-pharmaceutical companies.

Theracel Corporation, Rockville, Maryland
November 1984 to December 1990
Co-Founder of American Biotechnology Company (November, 1984)
Research manager, novel immune modifiers for treatment of cancer and inflammation. Acquired by Theracel in April, 1987

CooperBiomedical, Inc., Malvern, Pennsylvania
March 1984 to November 1984
Assistant Project Manager, serological based rapid detection diagnostic tests.

Wills Eye Hospital, Philadelphia, Pennsylvania
April, 1982 to March 1984
Research Associate, basic and clinical immunology & oncology research

University of Delaware, Newark, Delaware
September 1981 to May 1982
Research Assistant, Animal Sciences, immunology and virology

SPECIALTY & BIO-PHARMACEUTICAL EXPERIENCE

Lyotropic Therapeutics, Inc., Ashland, Virginia
Vice President, Business Development, July 1999 to present
Chief Medical Officer, February, 2006 to present

SafeScience Inc., (SAFS-NASDQ), Cambridge, Massachutsets
Director, Corporate Board of Directors, April 1998 to July 1999

IGGI, Cambridge, Massachussets
Scientific Advisor & Capital Acquisition, October, 1995 to April, 1998

RxAlliance, Richmond, Virginia
Product development & licensing consultant, January 1991 to present

EDUCATION

Ross University School of Medicine, *Dominica, BWI & New York, New York*
1991 to 1995

University of Delaware, *Newark, Delaware*
1976 to 1981

STATE LICENSURE

State of South Carolina,	active (Federal & State DEA License active)
State of Maryland,	active
Commonwealth of Pennsylvania,	active
Washington State,	inactive, 2004

PROFESSIONAL ASSOCIATIONS

American Society of Anesthesiologists
American Society of Regional Anesthesia
South Carolina Society of Anesthesiologists
South Carolina Medical Association
American Association of Pharmaceutical Scientists
Controlled Release Society
Licensing Executives Society

HOPSPITAL & CLINICAL COMMITTEES

Waccamaw Community Hospital:
Pharmaceutical & Therapeutics Committee, September 2003 to present
Physicians Quality Improvement Committee, July 2004 to present
Operating Room Committee (founder) October 2003 to present
JACHO Compliance Committee, (OR, ICU) July 2004 to present

Carolina Pines Regional Medical Center:
Pharmacy & Therapy Committee, July 2001 to July 2003

PATENTS, ISSUED & PENDING

Treatment using dantrolene, US Pat App Ser No 10/788,413.

Treatment Methods with low dose longer acting formulation o f local anesthetics and other agents, US Pat App Ser. No. 10/960,746

Stabilized Uncoated Particles of Reverse Liquid Crystal Phase Material, PCT Pat App WO 2005/034872.

Compositions for the reversal and detoxification of anesthetics and other compounds and methods of their use, US Provisional Pat App 60/868,950

PUBLICATIONS & ABSTRACTS

Novel Nanostructured Bupivicaine-Laden Particles Prolong Nerve Conduction Blockade Without Dose Increase. D. Anderson, Ph.D. and B. Cameransi, MD. NSTI Nanotechnology Conference. Boston, MA June, 2008

Neurogenic Pulmonary Edema; A case study. B.G. Cameransi, M.D. American College of Physicians. Baltimore, MD April 1996

Immunorestorative capability of Furylbutyrolactone and Ketobutyrolactone analogs in Cyclophosphamide suppressed mice. R.W. Veltri, P.E. Maxim and B.G. Cameransi. FASEB 2:912, 1988

Combined chemo- and immunotherapy of murine L1210 Leukemia with 5-Fluoruracil and the immunomodulator Methylfurobutyrolactone. P.E. Maxim, M.W. Baseler, M.R. Klinger, B.G. Cameransi and R.W. Veltri. Fed Proc 46:1512, 1987

Potentiation of the activity of anthracycline anticancer agents by L-Ascorbic Acid. R.W. Veltri, P.E. Maxim, M.R. Klinger and B.G. Cameransi. Proc Amer Assoc Canc Res 27:241, 1986

L-Ascorbic Acid (vitamin C) augmentation of anticancer activity of methoxy-substituted benzoquinones, adriamycin and dihydroxylated amino substituted quinine (DAHQ). Veltri RW, Maxim PE, Baseler MW, Cameransi BG, Klinger MR. Cancer Research, 1987

Enhancement of B-cell Activity Using the Methylfurobutyrolactones, a New Group of Biologic response Modifiers. P.E. Maxim, R.W. Veltri, M.W. Baseler and B.G. Cameransi. Fed Proc 45:495, 1986